**A. Scientific background**

Hoarding Disorder (HD) is a common and disabling public health problem. HD is a new diagnostic entity in DSM-5, affecting 44 million individuals in Europe alone (4% prevalence). HD is characterized by difficulty discarding items irrespective of their value, that accumulates to clutter and precludes normal use of living spaces, causing significant distress or impairment (Fig. 1) 1. Clutter accumulation leads to hazards such as fire, pest infestation, and eviction 2. While HD patients present aberrant neurocognitive and emotional processes, HD mechanisms remain elusive. Sleep disturbance hinders healthy adults’ neurocognitive and emotional processes which are aberrant in HD. Our preliminary results indicate that HD patients’ subjective sleep is worse than healthy participants (Fig. 2). It is unknown which objective sleep parameters impact HD and whether modifying sleep affects HD symptoms. The current project will mitigate these gaps and expose sleep disturbance’s role in HD by assessing 1) how objective and subjective sleep impact HD symptoms, neurocognition and emotion, and 2) test whether modifying sleep impacts clinical symptoms and cognition. We will refine HD’s neuropathological underpinnings and apply a scientifically informed sleep therapy for HD.

HD is a disabling and understudied disorder. Hoarding Disorder is a new diagnostic entity with four defining features; Patients are a) difficulty to discard objects irrespective of their values b) due to perceived importance, c) which leads to clutter accumulation limiting use of living spaces and d) causes significant distress or impairment. Most patients also acquire excessive items 1. HD impacts patients, their families and society – it is stigmatized, increases risks for chronic disease, pest infestations and fire hazards. HD patients exhibit abnormal neural activity in cognitive control and saliency circuits; the cognitive control network supports efficient resolution of simple conflicts and inhibition of prepotent actions 3,4. HD patients display hyperactivations in major nodes of this network; anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), right inferior frontal gyrus (RIFG) and specific basal-ganglia nuclei. The saliency network adjusts arousal and attention based on stimuli’s perceived relevance; HD patients display hyperactivations in the ACC and insula, which are the main nodes of this network. HD patients also exhibit behavioral deficits in cognitive control, visual perception, and reaction speed. However, patients’ neurocognitive abilities have yet to be systematically tested and the neuroscientific findings had little impact on HD treatments.

**Fig. 1:** Clutter typical of hoarding disorder

Sleep disturbance impairs neural circuits which are relevant to HD. Sleep is central to physiological and mental functioning. Sleep disturbance impairs cognitive control and saliency networks, as well as attentional and emotional processes 5–8. Insufficient sleep is a common sleep disturbance 9 and restricting healthy adults’ sleep even for a single night, impairs cognitive control and attention 10. Converging imaging findings suggest that sleep restriction modifies neural activity and connectivity within cognitive control and saliency networks including DLPFC, RIFG 11, thalamus, insula and ACC 12. Rapid Eye Movement (REM) sleep has a unique role in regulating affective homeostasis and restricting REM sleep intensifies emotional reactivity towards positive and aversive stimuli 13. Norepinephrine (NE) activity modifies arousal, reaching lowest levels during REM sleep. Altering NE secretion during sleep affects arousal likelihood 14. REM sleep may recalibrate phasic NE levels in the following day 13. Locus coeruleus is a major NE secreting nucleus 15 and its innervations to PFC and to the insula exemplify how arousal level modifies cognitive control and increases stimuli’s saliency 16–18. REM sleep’s physiology modifies Insula and ACC reactivity to salient content 19 and may modify HD symptoms. Sleep disturbance modifies brain circuits which are impaired in HD and warrants studying HD patients’ sleep. It is unknown whether sleep restriction affects HD symptoms.

Hoarding disorder patients exhibit subjective sleep disturbance. Sleep is understudied in HD. HD patients’ symptom severity is correlated with insomnia symptoms 20. HD patients report worse sleep and more severe insomnia symptoms compared with a control group, even when controlling for depression, age, and gender (Fig. 2). These studies highlight sleep disturbance’s importance in HD, but all used subjective sleep measures and did not test associations between sleep disturbance and patients’ cognition. Combining objective sleep measures with cognitive and clinical assessments will shed light on HD’s neuropathology.

CBT reduces sleep disturbance. Insomnia symptoms are a common sleep disturbance 21 hindering cognition and decision making 22. They are defined as persistent difficulties to initiate or maintain sleep despite motivation and ability to sleep, causing distress or affecting daily life 23. Insomnia patients display distinct objective sleep parameters 24. CBT for insomnia (CBTI) is a first-line insomnia treatment 25. CBTI focuses on modifying insomnia-related beliefs and perpetuating behaviors with cognitive and behavioral interventions which include tackling environmental factors (Table 3). CBTI improves patients’ objective and subjective sleep as well as their daytime functioning 25,26. CBTI is efficacious when delivered online or with self-help apps and therapist support, allowing for rapid implementation in rural areas and during pandemics 27. CBTI has never been tested in HD patients.

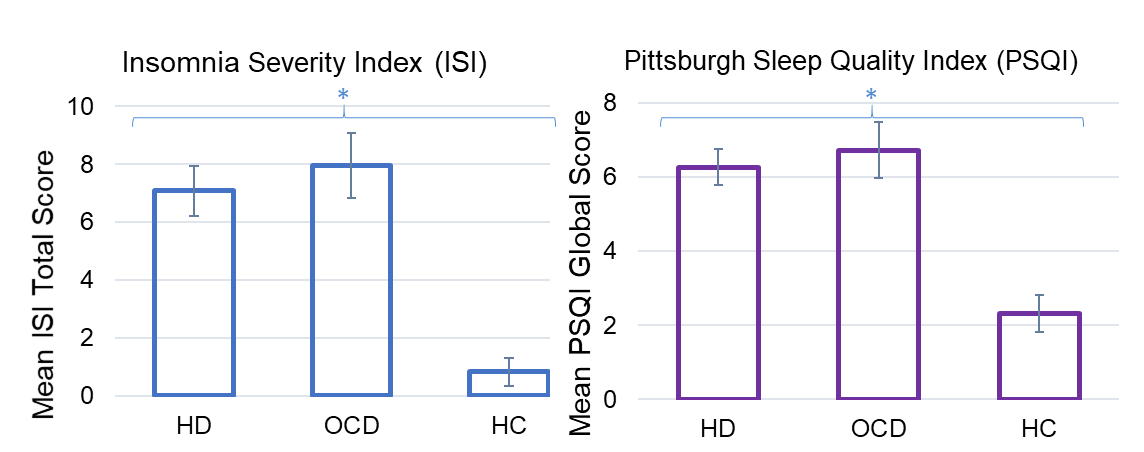


Fig 2. Mean ISI and PSQI scores in OCD (n=26), HD (n=38), and HC (n=22) 61, \*significance at .05 level. Error bars represent one standard error. ISI – insomnia severity index, PSQI – Pittsburgh Sleep Quality Index. Higher PSQI scores denote worse sleep quality

HD is difficult to treat. There are no FDA-approved drugs for HD. The leading cognitive-behavioral model of HD stipulates that symptoms result from distal factors (e.g., early experiences), cognitive deficits, and aberrant emotional responses which result in acquiring and difficulty discarding 28. Targeted cognitive behavioral therapy (CBT) and peer workshops are efficacious 29–31, however most patients continue to suffer from symptoms after completing treatments 32 and treatments’ acceptability is mediocre 33. Patients’ sleep disturbance may constrain treatment gains as it affects relevant brain circuits and indeed CBT for HD does not modify subjective sleep disturbance 34. There is an urgent need to develop new therapeutic interventions. Targeting HD patients' sleep may provide new therapeutic targets and refine HD’s underlying neuropathology.

## **Current experiment**

I suggest that sleep disturbance impairs HD patients’ saliency, cognitive control, and emotional neural circuits. Patients with aberrant saliency, reduced cognitive control and increased emotional reactivity will experience aggravated hoarding severity. The current study aims to mitigate scientific and clinical gaps in our understanding of sleep disturbance in HD and its interaction with cognition, emotion, decision making and clinical symptoms. I will test objective and subjective sleep patterns in a large sample of HD patients, a clinical control group of OCD patients, and healthy adults (phase 1). I will then assess how impairing (phase 2) and improving sleep (phase 3) alters patients’ cognition and clinical symptoms.

# B. Research objectives & expected significance

Sleep is imperative for mental and physical health. It affects neurocognitive processes which are central in HD. CBTI regulates these circuits 22. However, there are no objective sleep studies in HD and no studies testing how sleep interventions affect HD symptoms. This project’s overarching goal is to study the role sleep disturbance plays in HD by characterizing patients’ sleep and testing how two sleep interventions affect HD symptoms and patients’ cognition and clinical symptoms.

We need validated tasks to understand neurocognitive correlates of HD 35. Cognitive control differences between HD patients and healthy adults may result from lower level attention processes or arousal 36. We recently validated a new task teasing apart cognitive control and lower-level attention processes (Fig. 4). Our task allows testing which neurocognitive processes differ between HD, OCD, and healthy participants. We will also report which neurocognitive processes are correlated with symptoms severity. This project’s findings will lead to targeted brain imaging studies incorporating objective sleep and neurocognition.

Regulating sleep improves cognition and emotional processes 19,37,38. CBTI reduces depression 39 and improves cognitive control and saliency processing 22. Our study will be the first to test whether CBTI benefits HD and OCD patients’ symptoms and neurocognition while controlling for depression severity and age. Our results will have practical clinical implications - warranting sleep assessments during clinical intakes; suggesting sleep as a possible treatment target; and guiding future studies integrating CBTI components within existing HD and OCD therapies. Such advances can drastically improve patients’ lives. This research project will significantly advance our mechanistic understanding of HD, OCD, and test a cost-effective sleep intervention.

## Specific aims

1) Testing which objective sleep parameters differentiate HD from OCD patients and healthy adults. Significance: Characterizing HD patients’ objective sleep can shed light on HD’s neuropathology. Using OCD patients and healthy participants as control groups will inform our understanding of Obsessive-Compulsive and Related Disorders and test specificity of our findings.

2) Testing which objective sleep parameters are associated with clinical symptoms and core neurocognitive processes in HD. Significance: Conducting within-group analyses while controlling for depression severity and age will test the clinical significance of aim 1’s findings and guide development of novel, personalized treatments.

3) Assessing whether modifying sleep affects patients’ sleep, cognition, and clinical symptoms. Significance: If sleep deprivation impairs HD symptoms and CBTI improves HD symptoms, sleep will become a modifiable treatment target. Sleep interventions are cost-effective, and their dissemination will help numerous individuals struggling with HD.

4) Assessing which patients are more susceptible to sleep modifications. Significance: identifying HD and OCD patients which are more affected by sleep deprivation and benefit from CBTI may improve treatment personalization and facilitate future clinical trials.

**C. Detailed description of the proposed research**

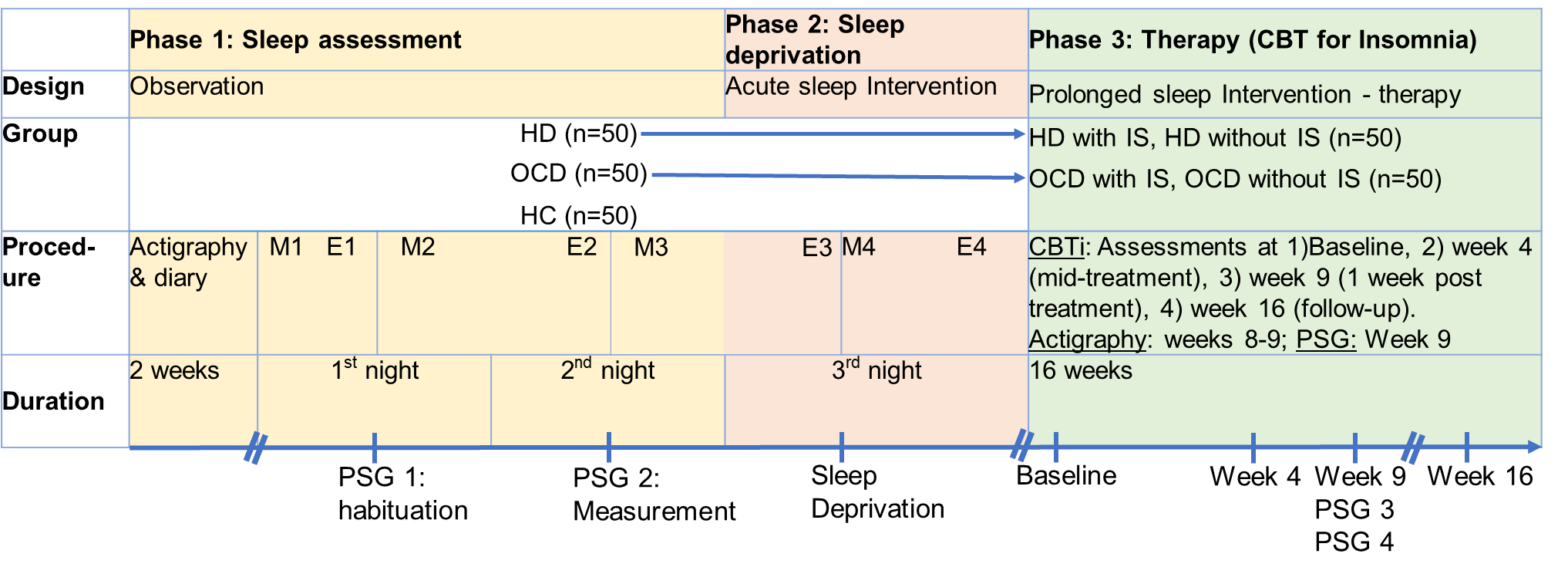
## **General working hypothesis**

HD patients report increased sleep disturbance compared to healthy participants (Fig. 2). In healthy participants, such disturbance affects neural circuits which are imperative in HD: cognitive control, emotional reactivity, and saliency processing. We hypothesize that sleep disturbance and specifically REM sleep duration or REM stability, exacerbate HD by affecting these neural circuits and their behavioral correlates. We will test our hypothesis in 3 phases: 1) Comparing objective and subjective sleep and central neurocognitive processes in HD patients, OCD patients and healthy participants; 2) Testing whether inducing sleep disturbance impacts patients’ clinical symptoms and central neurocognitive processes; 3) Testing whether CBTI improves HD and OCD patients’ symptoms, sleep and neurocognition. Together, our results may constitute a major advance the field of HD and OCD, enrich evolving research of sleep and neuroscience of obsessive-compulsive and related disorders and lead to follow up neuroimaging studies and clinical trials.

## **Research design & methods**

All studies will be approved by Bar-Ilan University’s Internal Review Board and the collaborating mental health clinics’ Helsinki committees prior to study initiation. Any medical findings will be reported to patients and to their treating physicians.

### **Phase 1: Testing objective and subjective sleep**

Participants and recruitment strategy: 150 participants (ages 18-65); 50 HD, 50 OCD, 50 Healthy controls (HC) will participate in phase 1. HD and OCD patients will be recruited from major mental health centers and clinics (letters attached) and advertisements in the media (see budget). HC will be recruited through targeted social media advertisements, flyering and emails to all Bar-Ilan University’s staff members. Inclusion criteria: all groups – ability to complete study procedures. HD – primary HD diagnosis, determined with the Diagnostic Interview for Anxiety Mood and Obsessive-compulsive and related Disorders (DIAMOND), validated by a gold-standard self-report scale; Savings Inventory Revised (SIR) score ≥ 41 30. OCD – primary OCD diagnosis determined by the DIAMOND and validated by a Yale-Brown Obsessive-Compulsive Scale (YBOCS) score ≥ 16. HC – ability to complete study procedures. Exclusion criteria: all groups – history of severe head trauma or neurological conditions. OCD & HD – A. Psychosis spectrum disorders, moderate and severe substance use disorders, co-morbid HD and OCD; B. Hamilton Depression Rating Scale 17 (HDRS-17) score > 19; C. Active suicidality determined by the Columbia Suicidality Severity Rating Scale (CSSRS); D. current CBT for HD or OCD; E. changes in pharmacotherapy in the past month; F. Regular benzodiazepines use. HC – A. current or history of any psychiatric or sleep disorders determined by the DIAMOND and SCID modules; B. regular consumption of arousal-regulating pharmacotherapy or drugs.

Week 8

PSG 3

PSG 4

Week 16

Fig. 3: Project outline post screening. M - morning, E - evening. Participants will complete neurocognitive and clinical measures at M1-M4 and E1-E4 as well as weeks 0, 4, 9, 16 of phase 3.

Procedure:

Screening. Once a potential patient is identified, research staff members will conduct a short phone screening describing the study and validating inclusion and exclusion criteria with general questions. Eligible participants will attend a screening session at Bar-Ilan University or in the referring clinic. At the screening session participants will review and sign informed consent. Participants will complete semi-structured interviews, self-report measures (Table 1) and short neurocognitive tasks (Fig. 4-6). Research staff will provide participants with actigraph watches. Actigraphy. Participants will wear actigraphs and fill in sleep diaries for 2 weeks, validating actigraphy results (Tables 1,2). Actigraphs measure objective sleep, daily activity and bedroom luminance with high ecological validity 40. PSG. After 2 weeks, participants will complete 2 consecutive PSGs at Hadassah Medical Center’s sleep center (letter attached). The second night will control for a ‘first night effect’ - altered sleep patterns during a first night in a sleep center. Participants will receive summary reports. Aberrant findings will be sent to their physicians.

Measures:

Clinical & self-report. We employ minimal and clinician-administered assessments to assess

inclusion and exclusion criteria. Our self-report measures have good psychometric properties and are the most common tools to study our target constructs (Table 1).

|  |  |  |
| --- | --- | --- |
| **Assessment** | **Target construct** | **Reference** |
| **Clinician Administered** |  |  |
| DIAMOND | HD, OCD, major psychopathologies | 41 |
| SCID sleep module | Sleep disorders | 42 |
| YBOCS | OCD severity | 43 |
| HDRS | Depression severity | 44 |
| CSSRS | Suicidality | 45 |
| **Patient Rating – Clinical** |  |  |
| SI-R | Hoarding severity | 46 |
| CIR | Clutter severity (image rating; Fig. 1) | 47 |
| OCI-R | OCD severity | 48 |
| DOCS | OCD dimensions | 49 |
| DASS | Depression, Anxiety, Stress | 50 |
| **Patient Rating – Sleep** |  |  |
| ISI | Insomnia Symptoms Index | 23 |
| PSQI | Sleep quality, Sleep Phase | 51, 52 |
| ESS | Daytime sleepiness | 53 |
| FOSQ | Sleepiness' impact on quality of life | 54 |
| ME | Circadian type | 55 |
| Consensus sleep diary a | Sleep patterns b | 56 |
| Table 1: Screening measures details. Clinician administered: DIAMOND - Diagnostic Interview for Anxiety Mood and Obsessive Compulsive and related disorders; SCID - Structured Clinical Interview DSM- 5; YBOCS - Yale-Brown Obsessive Compulsive Scale; HDRS - 17-Item Hamilton Depression Rating Scale; CSSRS - Columbia Suicidality Severity Rating Scale | | |
| Patient rating - clinical: SI-R - Savings Inventory Revised; CIR - Clutter Image rating; OCI-R - Obsessive Compulsive Inventory Revised; DOCS - Dimensional Obsessive-Compulsive Scale; DASS - Depression Anxiety Stress Scale. | | |
| Patient rating - sleep: ISI - Insomnia Severity Index; PSQI - Pittsburgh Sleep Quality Index; ESS - Epworth Sleepiness Scale; FOSQ - The Functional Outcomes of Sleep Questionnaire; ME – Morningnesss\ Eveningness. a We will add 2 items about medications, alcoholic and caffeinated drinks consumed in the previous day. b Participants will fill this out daily for 2 weeks. | | |

#### Objective Sleep.

*Actigraphy.* Phillips PRO actiwatch tracks movements for up to 30 days consecutive days with a sampling rate of 32Hz. Raw activity scores (in 1-min epochs) are translated to sleep-wake scores based on validated computerized scoring algorithms resulting in bedtime, time in bed, total sleep time, sleep onset latency, wake after sleep, arousals number and sleep efficiency as well as daytime activity. This Actigraph is waterproof, and its battery supports 30 consecutive recording days, so participants can wear it consecutively throughout the study.

*PSG.* This device records electrical activity in scalp (EEG), eyes (Electrooculography), muscles (Electromyopgraphy), as well as expiratory/inspiratory nasal airway pressure, nasal/oral airflow, finger pulse oximetry, electrocardiogram, rib cage and abdomen movements, snoring, and body position. Sensors are placed, calibrated, and signal quality is checked by a research technician.

|  |  |
| --- | --- |
| **Assessment** | **Target construct** |
| **General Sleep measures** |  |
| Total sleep duration | Total time spent asleep |
| Sleep latency | Time taken to fall asleep |
| Time in bed | Amount of time in bed |
| Sleep efficiency | Sleep duration divided by time in bed |
| N1, N2, N3, REM proportion | Total time spent in each phase relative to general sleep time |
| Arousal index | Number of arousals |
| Wake after sleep onset | Time spent awake between sleep onset and final awakening |
| **REM & motor measures** |  |
| REM latency | Duration from first sleep epoch to first REM epoch |
| REM stability a | Proportion of arousals during REM |
| REM without atonia | Duration of REM with muscular activity |
| REM density | Average number of eye movements during REM |
| Periodic limb movement index | Index of limb movements and periodic limb movement series |
| LM & PLMS arousals | Number of arousals due to motor movements |
| **Respiratory measures** |  |
| Apnea Hypopnia Index | Compound summary of apnea and hypopnea events |
| Respiratory distress index | An index assessing overall respiratory distress |
| Overall desaturation index | Overall number of oxygen desaturation events |
| Minimal desaturation | Minimal oxygen saturation throughout the night |
| **Spectral analysis** |  |
| Relative power | Power of each frequency band divided by total power |
| Table 2: Main PSG measures and target constructs. REM – Rapid Eye Movement; LM – limb movements; PLMS – Periodic Limb Movement in sleep | |

PSG will be manually scored by Drs. Alex Gileles-Hillel and Dr. Joel Reiter, board-certified sleep physicians experienced in scoring PSG in line with American Association for Sleep Medicine guidelines (AASM; Table 2) (letter attached). Physicians will be blinded to participants’ group.

#### *Neurocognitive*.

*Attentional Networks Test-Dissociation (ANT-D).* ANT-D measures efficiency of 3 major attentional networks – cognitive control, alertness, and orienting. Participants manually report the color of a single arrow (Fig. 4). Using a single arrow allows to dissociate interactions between orienting and alerting 57. Healthy participants demonstrate 3 significant main effects for 3 attentional networks with no interactions between the networks (Fig. 4). Primary outcome measures is reaction times (RT) difference between levels of each condition (e.g., incongruent and congruent).

*Emotional reactivity task*.This task measures efficiency of disengaging from emotional images. Participants indicate a central arrow’s direction, while disregarding distracting flanker arrows (Fig. 5). A negative or a neutral image are presented before the arrows 58. Primary outcome measure is emotional interference (i.e., emotional reactivity), calculated by subtracting RTs of correct answers following neutral images from RTs of correct answers following negative images.

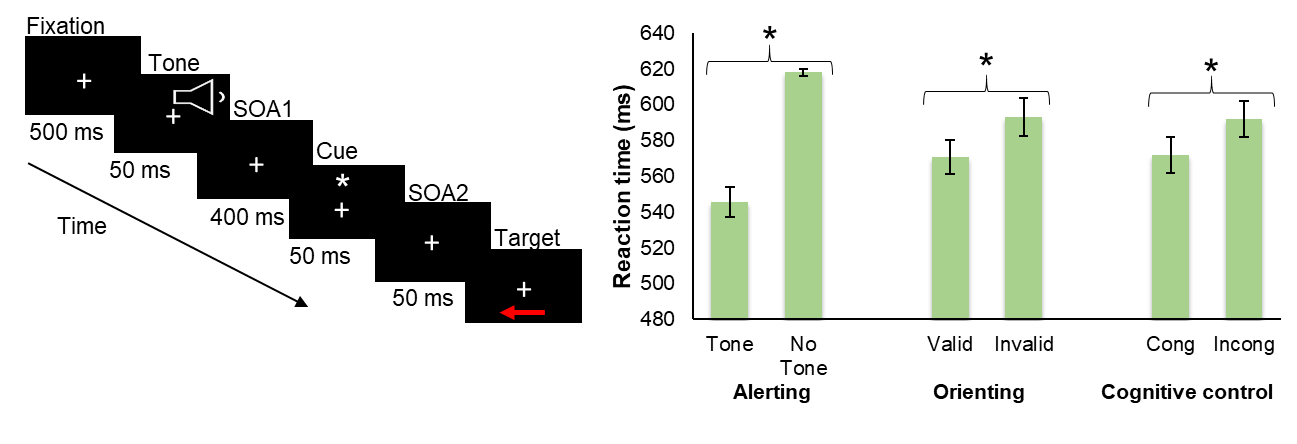
*Monetary incentive delay (MID)*.MID measures responses to potential monetary rewards and losses. Participants respond to a target stimulus before its disappearance at a predefined cutoff (Fig. 6). Prior to stimulus presentation, a cue specifies how much money will be gained or lost if the participant responds faster than the cutoff. Participants learn the amount associated with each cue before the task. Primary outcome measure is a slope of RT change as a function of cue’s value. RT decreases when cue value increases. The magnitude of this decrease is a measure of motivation. Since the measure is a difference-score, it is not confounded by psychomotor speed.

Fig. 4: ANT-D. Participants respond to an arrow’s color (red\ blue). The button for red color is located on the right (‘m’) and the button for blue color is on the left (‘c). Alertness is modulated by playing a brief tone, (50ms, 2000 Hertz) in 50% of trials. Orienting is modulated with a visual cue – an asterisk appearing in a valid (50% of trials) or invalid location compared to the following arrow’s location. Congruency is modulated by the irrelevant arrow’s direction, which can be congruent or incongruent with the response button. A) An alerted, invalid trial. B) Results from healthy participants (n=22). Error bars represent one standard error. Cong- congruent; Incong- incongruent. (Linkovski et al., in prep). \* indicates p value < .05. Effect sizes: alerting ηp2 =.59, orienting ηp2 =.28, cognitive control ηp2 = .22. There were no significant interactions.

*Stroop task*. The Stroop task is a hallmark cognitive control measure 59. Participants manually respond to a word’s ink color while inhibiting semantic information which emerges from reading the word. The color and semantic meaning can be congruent (e.g., “Red”) or incongruent (e.g., “Red”). Primary outcome measure is the congruency effect – reaction time difference between congruent and incongruent conditions. The congruency effect has good test-retest reliability during multiple administrations within short time spans as our study 60. Participants will complete it at screening and once after the 2nd PSG night.

**Fig. 5**: Emotional reactivity task illustration. Patients indicate a square’s color (green\ blue) preceded by emotional or neutral image

Fixation

1,000 ms

100 ms

Image

Blank

Discrimination

50/100 ms

1,000 ms

Time

+



#### Statistical analysis & expected results:

#### We will first characterize age, gender, depression, and stress differences between groups, with either independent sample t-tests or Mann–Whitney tests. We will also report sleep disorders’ rates across groups. Below are our main analyses per testing domain.

##### *Analysis & expected results*: *Subjective sleep measures*

Power analysis: Based on our preliminary data (Fig. 2) current sample size will enable over 95% power to detect a medium to large effect size with a type one error of .05. Expected results: We hypothesize that HD and OCD will have greater sleep disturbance ( ISI and PSQI global scores), with more severe fatigue (ESS scores) and reduced daytime functioning (FOSQ scores). We anticipate higher rate of eveningness tendencies in OCD compared with HD and HC, as in our preliminary data 61.

**Fig. 6.** Illustration of a monetary incentive delay trial. Cue predicts the amount that can be gained or lost.

Cue

250 ms

2-2.5 sec

Delay

Target

Outcome

160-260 ms

1,450 ms

+5.00

[25.00]

Time

##### Analysis & expected results: Objective sleep measures

*Actigraphy.* We will test differences in mean and intra-individual variability of sleep duration and efficiency using the location-scale mixed model - an extension of hierarchical linear models approach allowing to simultaneously analyze the mean and interpersonal variance while accounting for missing data. It also enables testing group variance differences over and above mean values 62. Sleep efficiency\duration will be dependent variables, daily data will be treated as nested within subjects. Group (HD, OCD, HC) will be the independent variable. We will also compare groups’ frequency differences in delayed bedtimes and rise times with a chi-square test. *Power analysis*: There are no actigraphy studies in HD. We conducted a power analysis for actigraphy and PSG based on a recent OCD study (Donse et al., 2017). Our sample size will allow a power of 90% to detect medium to large effects using a type one error of .05. *Expected results:* We hypothesize that HD and OCD groups would exhibit greater intra-individual variance and reduced sleep efficiency. This would reflect a sparsely studied aspect of sleep disturbance in HD and OCD. We hypothesize that delayed bedtimes and rise times will be more prevalent in OCD compared with HD and HC.

*PSG*. We will test PSG data from the 2nd night. We will use Multiple Analyses of Covariance (MANCOVA) to compare sleep stages' duration, relative power for alpha-theta frequencies, sleep efficiency, apnea hypopnea index, PLMI index, and REM without atonia (RWA) rates between groups. Age, gender, and depression severity will serve as covariates, with crucial alpha adjusted for false discovery rate correction. We will test the clinical significance of PSG differences by conducting a linear regression with the significant group differences evidenced in the MANCOVA as predicting clinical severity when controlling for relevant covariates. We will use t-tests to compare rates of sleep disorders between our groups, including RBD, obstructive sleep apnea and parasomnias. Sensitivity analyses will test whether REM differences are due to serotonergic medications 64. *Power analysis*:There are no PSG studies in HD. We conducted a power analysis based on an OCD meta-analysis 65. Our sample size will allow a power of 90% to detect medium to large effects using a type one error of .05. PSG motor indices were not included in the meta-analysis but 72%-90% of OCD patients exhibit abnormal nightly movements 66,67. Expected results: We hypothesize that OCD and HD groups will demonstrate reduced sleep efficiency with more pronounced reductions in REM duration and stability. We hypothesize that the OCD group will exhibit elevated aberrant nightly movements - PLMI Index and REM without atonia, compared with the HD group as seen in pediatric OCD 66,67.

*Analysis & Expected results*: *Neurocognitive measures*

*ANT-D.* A three-way analysis of variance (ANOVA) will be used with alerting tone (tone, no tone), orienting cue (valid, invalid) and congruency (congruent, incongruent) as independent within subject variables, group (HD, OCD, HC) as a between subject independent variable and RT as the dependent variable. We will conduct a linear regression testing whether objective sleep efficiency, sleep duration and group predict the main effects of our 3 attention networks. *Power analysis*: The current sample allows for 85% power in detecting a medium size effect with a type one error of .05 based on a cognitive control study 68. Alertness and orienting have not been tested in OCD and HD and results will set a benchmark for follow up hypothesis-testing studies. Expected results:We anticipate that HD will have significantly larger congruency effect compared with OCD 69. We hypothesize that HD and OCD will demonstrate larger alerting effects and that across groups, alerting effects will be associated with sleep efficiency and duration.

*MID.* RTs will be analyzed by a repeated-measures ANOVA with cue (maximum loss, neutral, maximum gain) as a within-subject variable and group as a between-subject variable. Power analysis: This task has not been tested in HD. Our results will set a benchmark for follow up hypothesis-testing studies. Expected results: In line with past studies, we hypothesize RT decreases as cue value increases. We hypothesize that HD patients exhibit lower difference range, as every cue is more salient to them than to HC, eventually reaching a ceiling effect. Therefore we anticipate HD patients exhibit less decrease with monetary changes and slower RTs to lower value cues compared with OCD and HC, which exhibit comparable RTs in this task 70.

*Emotional reactivity*. An ANCOVA will assess group differences, with emotional interference index as the dependent variable, group (HD, OCD, HC) as the independent variable, and depression severity and age covariates. Regression analysis will test association between sleep parameters and this task’s outcomes. Sensitivity analyses will control for serotonergic medication confounds. Power analysis: This task yielded large effect sizes in HC 58. Comparing HD and HC on subjective distress in emotional reactivity scales also yielded large effect sizes 71, suggesting that our sample size allows for 95% power to detect medium to large effect sizes. Expected results:We hypothesize that HD would display heightened emotional reactivity compared with OCD and HC. We hypothesize that across HD and OCD, sleep quality and REM stability would predict emotional reactivity.

*Stroop.* An ANCOVA will assess group differences, with congruency effect as the dependent variable, group as the independent variable, and depression severity and age as covariates. Regression analyses will test which sleep parameters are associated with congruency effect. These results will be corroborated by running hypothesis-driven analyses on congruency effect in the ANT-D. Power analysis: The current sample allows for 85% power in detecting a medium size effect with a type one error of .05 68. Expected results:We hypothesize that HD will exhibit a larger congruency effect compared with OCD and HC, corroborating ANT-D’s findings.

## Phase **2: Testing sleep deprivation effects on neurocognition and clinical Symptoms**

Working hypothesis: It is unknown whether sleep disturbance precedes clinical symptoms, results from these symptoms, or whether more complex interactions exist. We aim to test whether experimentally modifying participants’ sleep can affect disorder-relevant neurocognitive processes and clinical symptoms. We hypothesize that a) a night of sleep deprivation will enhance neurocognitive differences between HD, OCD and HC; b) these neurocognitive differences would predict clinical symptoms during the following day; These results would lead to follow up studies examining which sleep stages or electrophysiological activity during sleep is driving these changes.

Participants: Same as Phase 1 (Fig. 3).

Procedure: After completing phase 1 (Fig. 3) participants will return to the sleep center during the afternoon to perform the same neurocognitive tests and brief clinical assessments as in phase 1. Then they will spend 24 hours awake in the sleep center, while engaging in recreational activities of their choice. They will complete the same neurocognitive measures upon in the following morning and evening. Participants will refrain from napping until final assessments.

Methods: See phase 1.

Statistical analysis & expected results:

General approach: We will minimize psychomotor training effects by limiting cognitive testing sessions and by conducting between-group comparisons in change scores pre- and post- sleep deprivation. We reduce non-specific improvements due to task familiarity by including an initial training in all tasks during phase 1’s screening. We will reduce stimulus familiarity by modifying perceptual task features in each session – colors in ANT-D and Stroop, shapes in the MID, and images in the emotional reactivity task. The Stroop task will validate effects in our cognitive battery with only 3 repetitions in phases 1-2. Our tasks show good test-retest reliability in healthy participants 58,72,73. Our design evaluates test-retest reliability in HD and OCD and will enhance our findings’ validity. Secondary analyses will compare between-group changes from evening pre- to evening post-deprivation. All analyses will control for gender, depression, stress, and age. Power analysis: sleep deprivation leads to large effect sizes on neurocognition, but no studies tested them in HD or OCD. Our study will set a benchmark for future hypothesis-testing trials. We will conserve statistical power by only analyzing variables which differ between HD and HC in phase 1. Regression analyses will test whether habitual sleep efficiency and duration (phase 1) predict changes in each task’s main outcome measure (specific aim 4).

*ANT-D*. A MANCOVA will be used with changes in alerting, orienting, and congruency as dependent within-subject variables, time (pre-, post- sleep deprivation) as a within-subject independent variable, and group (HD, OCD, HC) as a between subject independent variable. Expected results:We anticipate that HD and OCD groups will exhibit larger changes in all attentional networks compared to HC. These results will be more pronounced following sleep deprivation.

*Stroop*. We will test between-group differences in congruency effect with an ANCOVA. Congruency effects as the dependent variable, and group and time as independent variables. *Expected results*: HD will demonstrate larger congruency effect compared to HC and OCD. This interaction will be more pronounced following sleep deprivation.

*MID*. Reaction times changes will be analyzed with a repeated measures ANCOVA with cue (maximum loss, neutral, maximum gain) as a within-subject variable, time as a within subject independent variable, and group as a between-subject independent variable. Expected results: In line with previous studies 74 we anticipate an interaction between group and cue so that HD participants will exhibit larger differences in the gain vs. neutral cues compared to OCD and HC. We anticipate this interaction will be larger following sleep deprivation, suggesting that sleep deprivation increases sensitivity to rewards in HD.

*Emotional reactivity*. An ANCOVA will assess group differences, with emotional interference change index as a dependent variable, group and time as independent variables. Expected results: We hypothesize that HD would display heightened emotional reactivity compared to OCD and HC groups and that this interaction will be larger post-sleep deprivation.

## **Phase 3: Can Improving Sleep Affects Clinical Symptoms and Cognition**

Working hypothesis: We hypothesize that sleep disturbance exacerbates HD and OCD symptoms and that improving patients’ sleep will benefit patients. This feasibility study will be the first to test whether targeting patients’ sleep disturbance with CBTI, an evidence-based insomnia psychotherapy, is feasible and acceptable. We hypothesize that CBTI would improve patients’ sleep, clinical symptoms, and cognition.

Participants and recruitment strategy: HD and OCD patients who complete phase 2. Pending enrollment rates at 12 months, we will add recruitment efforts and enroll HD and OCD patients experiencing clinically significant insomnia symptoms to this phase alone. Our preliminary data suggests a high prevalence of clinically significant insomnia symptoms in HD (24%) and OCD (27%) 61. Patients will be divided to subgroups based on their insomnia symptoms (Fig. 3). Patients reporting clinically significant insomnia symptoms (ISI > 10) will be assigned to CBTI groups, and remaining patients will constitute clinical control groups. Inclusion criteria: Same as phase 1. Exclusion criteria: Same as phase 1 and untreated objective sleep disorders identified at phase 1.

Procedure: Participants will complete a standard 8-weeks CBTI course with special emphasis placed on environmental factors to HD such as bedroom clutter (Table 3). Participants will repeat phase 1’s neurocognitive and self-report measures at: A) baseline, B) mid treatment (week 4), C) one week post treatment (week 9) and D) 2 months post treatment (week 16). They will complete 2 weeks of actigraphy during the final weeks of treatment (weeks 8-9) and two PSG nights at Hadassah Medical Center (Week 9) (Fig. 3). CBTI would be conducted by graduate-level psychologists under supervision and following in-person training. Prof. Rachel Manber, a CBTI expert who developed a national CBTI training initiative across Veterans Health Administration system, will oversee CBTI training and quality assurance (letter attached). Prof. Manber will also

train therapists on how to assess and address HD-related aspects of the sleep environment.

Measures: See phase 1 (Table 1; Fig. 4-6). We will add 2 self-report measures: 1) *Insomnia Treatment Satisfaction Scale (ITSS)* – assessing CBTI’s impact on insomnia, and 7 major life areas; energy level, work productivity, coping, life enjoyment, hopefulness, self-esteem, and mood 76. 2) *Treatment Components Adherence Scale (TCAS)* – assessing adherence to CBTI’s behavioral and cognitive components 77. Participants will complete the ITSS and TCAS upon treatment completion. Therapists will report environmental factors affecting participants’ sleep.

|  |  |
| --- | --- |
| Session | Main content |
| **1** | Assessment: Sleep history, habits, cognitions, and environmental factors such as bedroom clutter. Review phase 1’s sleep diaries |
| **2** | Psychoeducation & behavioral techniques: Main techniques are 1) stimulus control, e.g., leaving bed when not falling asleep; 2) Sleep restriction therapy, e.g., scheduling a regular sleep time; 3. Mitigating environmental factors, e.g., moving bed clutter to another room |
| **3** | Cognitive techniques & troubleshooting: 1) “constructive worry” – prescribing a pre-bedtime and writing worries and tangible actions to mitigate them. 2) thought record – standard CBT practice applied to sleep. Writing maladaptive sleep thoughts, their context, and associated emotions. We will work on creating alternate adaptive beliefs |
| **4-5** | Review of sessions 2-3 & modifications to behavioral and cognitive techniques |
| **6** | Summary & future action plans |

Table 3: Current CBTI’s main procedures per session, emphasizing environmental factors 78.

Statistical analysis & expected results:

General: All analyses will use the intent-to-treat principle and include all participants who started CBTI with their last observation carried forward. Power analysis: This would be the first study testing CBTI in HD and OCD. Outcomes will guide power calculations for follow up hypothesis-testing trials.

Insomnia symptoms: Two ANCOVAs will compare ISI pre- and post- treatment in HD and OCD, with ISI scores as a dependent variable, time (baseline, post-treatment) and treatment (CBTI, no treatment) as independent variables and age and depression severity as covariates. Separate mixed-effects regression models will test ISI change over time. Expected results: we hypothesize that both HD and OCD patients will demonstrate reduced insomnia symptoms following CBTI.This would represent a novel therapeutic and conceptual advancement in treating HD and OCD since patients’ sleep is not addressed in existing treatments.

Treatment feasibility and acceptability. *Completion rates,* TCAS and ITSS scores will be reported in line with previous treatment development studies 76. Expected results: We hypothesize high treatment feasibility and acceptability in HD and OCD.

Clinical measures: We will test CBTI’s impact on HD and OCD outcomes by using 2 ANCOVAs with the clinical variable — SIR for HD and YBOCS for OCD — as a dependent measure, time (baseline, mid-treatment, post-treatment, follow-up) and treatment (CBTI, no treatment) as independent measures. Number of responders in each group will be reported, using an a-priori criterion of 35% improvement 79. Expected results: We hypothesize that CBTI will reduce HD and OCD severity and that this reduction will persist over 2 months. If successful, and pending replication, our results may constitute a new treatment option for HD and OCD patients and lead to follow up treatment-development studies integrating CBTI and CBT for HD and OCD. Integrating CBTI and CBT yielded positive results in different fields 80.

Neurocognitive processes: 3 repeated-measures ANCOVAs for HD and OCD will be used for ANT-D, MID and emotional reactivity task with RTs as dependent variables, time (pre-treatment, post-treatment), and treatment (CBTI, control) as independent variables. All analyses will control for age, gender, and depression severity. Expected results: We hypothesize that CBTI will increase alerting effect in the ANT-D task in both groups, reduce loss sensitivity of HD participants in the MID, and decrease emotional reactivity in OCD and HD CBTI groups compared to their control group.

Subjective sleep measures: a 3-way ANCOVA will be used with sleep scores as dependent variables (PSQI, ESS, FOSQ), time (baseline, mid-treatment, post-treatment, follow-up), group (HD, OCD) and treatment (CBTI, no treatment) as independent variables. Expected results: We hypothesize that sleep quality and daytime functioning will increase in HD and OCD.

Objective sleep measures: Actigraphy & PSG: *Separate* repeated measures ANCOVAs will be used to test whether CBTI modifies HD and OCD patients’ aberrant sleep parameters detected in phase 1. Independent variables will be time (baseline, post-treatment) and treatment (CBTI, no treatment). Depression severity and baseline clinical severity will be the covariates. Expected results:We hypothesize that CBTI will improve objective sleep measures in HD and OCD groups.

Facilities & personnel

Dr. Linkovski is an experienced psychologist, focusing his clinical and scientific efforts in studying HD and OCD. He has been assessing and treating patients suffering from these psychopathologies in the past 9 years including training from experienced professionals on clinical assessments (Prof. Anthony Pinto), CBT and therapeutic interventions for HD and OCD (Prof. Gideon Anholt, Dr. Anthony Lombardi, Mr. Lee Shuer). Dr. Linkovski completed a postdoctoral fellowship at the department of Psychiatry and Behavioral Sciences at Stanford University where he focused on advanced clinical training, large scale clinical trials (Prof. Carolyn Rodriguez) and basic sleep research (Prof. Ruth O’hara. Prof. Makoto Kawai). Dr. Linkovski has mentored over 25 graduate and undergraduate students in the past 6 years in clinical and research settings. In the past year Dr. Linkovski initiated his lab at Bar-Ilan University and is mentoring graduate and undergraduate students who are setting up the proposed study, as well as clinicians who will serve as independent evaluators. Dr. Linkovski’s lab includes 3 experimental rooms with the required software and hardware and 3 shared clinical interview rooms. Bar-Ilan University allocated space to open its sleep center. I am submitting an additional ISF equipment grant to purchase a PSG. An ISF-funded sleep lab will simplify participant access, reduce costs, and expand PSG usage. I will train graduate students in sleep scoring while maintaining support from Drs. Reiter and Gileles-Hillel. Prof. Rachel Manber, a CBTI expert, will assist in CBTI implementation and quality assurance. Dr. Linkovski is collaborating with Prof. Rodriguez on several ongoing neurocognitive and clinical projects pertaining to HD and OCD, as well as PSG studies in pediatric OCD with Profs. O’hara and Kawai. He is conducting the first study testing whether a neurosurgical procedure for OCD affects sleep with Prof. Hagai Bergman and Dr. Renana Eitan (Hebrew University). These global leaders will be available for ad-hoc advice on theoretical and practical aspects of this study.

Potential pitfalls and contingency plans

Recruitment: Recruiting 3-4 patients a month is sufficient and expected based on our experience in recruiting HD and OCD patients. There is no HD research or Israeli psychologists who specialize in HD and therefor our initial patient pool might be small. However, HD is equally prevalent across societies 81–83. To maximize recruitment rate, we are collaborating with one of the largest Medical Centers for mental health in Israel - the Jerusalem Center for Mental Health (over 2,300 patients), a large, specialized CBT center (“Cognetica”) and Bar-Ilan University’s clinic. In addition, we will recruit participants using social media and local newspapers. We will contact additional Israeli clinics and medical centers as needed. Having the same participants completing phases 1-3 will allow for longitudinal analyses and enhance statistical power. We will assess enrollment yearly and consider recruiting different patients for each phase. Meeting recruitment goals will allow us to test our primary hypotheses, driving future randomized clinical trials and longitudinal studies.

Participant characteristics: Menstrual cycle may affect sleep. We will ask female participants to indicate time since their period. This will be used to optimize scheduling and for post-hoc analyses. However, we will not exclude participants who do not provide this information.

Covid-19: the covid-19 pandemic impacted clinical research limiting in-lab sessions. I will mitigate the following ways: 1. Subjective questionnaires and clinical interview reports will be completed on Qualtrics’s secured system. HIPPA approved zoom license will be purchased to conduct remote clinical interviews and CBTI sessions. 2. Our neurocognitive tasks are built with ‘Eprime’, allowing accurate data collection. Research staff will deliver participants identical laptops and sanitize them after each use. 3. Actigraphy – we will sanitize actigraphs between participants according to manufacturer guidelines we received. 4. PSG – In case of extensive quarantine (over 6 weeks) during the study period we will consider using PSG at participants’ homes or mobile sleep-staging devices 84. Dr. Linkovski administered 50 in-home PSGs in an ongoing study at Stanford University. Modifications will be approved by health authorities and review boards.

Study’s significance

1. Characterizing objective sleep in HD: our study will be the first to explore objective sleep in HD, while providing additional information on the diverging and converging sleep characteristics in Obsessive Compulsive and Related Disorders. This may improve our mechanistic understanding of sleep in HD and OCD and may guide treatment development.
2. Testing whether sleep modifications on participants’ sleep and clinical outcomes: testing how sleep modifications affect clinical symptoms and neurocognition will provide preliminary directional connections for sleep’s role in the etiology and or maintenance of these disorders.
3. Piloting a new therapeutic intervention: If CBTI proves efficient for HD and OCD, it may constitute an affordable, scalable intervention. This will lead to follow-up large scale research projects, grant applications, and most importantly - improving millions of lives.

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